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10/589,751	08/17/2006	Francese Giancarlo	705152-2001	9535

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EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,751	GIANCARLO ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-43 and 47-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-43 and 47-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-43 and 47-57 are pending .

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 08/27/2010 is acknowledged. Claims 28 , 29, 42 and 54 are amended. The claims 26-43 and 47-57 are under consideration in the instant office action.

Applicants' arguments, filed 08/27/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Rule 37 CFR 1.132 Declaration

Applicant's submission of the declaration by Dr. Fabrizia Marazza on 08/27/2010 is acknowledged. The declarations are, however, not found to be persuasive in light of the reasons set forth below in the response to arguments following the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection of Claims 28-43 and 47-57 under 35 U.S.C. 35 U.S.C. 103(a) as being unpatentable, under over Buchs et al. (US 5814635, reference already of record) in view of Mueller et al. (US 6160116) is maintained for reasons of record restated below.

Amendment to claim 28 has clarified the diastereoisomeric excess to be of at least 75%. Mueller teaches that the R form of folinate is not active and teaches method of preparing pure sodium (6S) folinate and further teaches the preparation of a sodium salt of (6S)-folinic acid having a purity of at least 95%. As such it would have been obvious to a person of ordinarily skill in the art to utilize the purified (6S) sodium folinate taught by Mueller et al. in the concentrated solution of Buchs et al. with the (6S) sodium folinate being at concentrations well over 75% in the solution.

Claims 29, 42 and 54 were amended to rectify the indefiniteness associated with these claims as pointed out in the non-final rejection dated 04/27/2010 and does not add any new limitations which is not addressed by the original rejection recited below.

Original rejection:

It is respectfully pointed out that claims 29-38 are product-by-process claims. As per MPEP section 2113 (R-1) product by process claims, even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113. Thus, because Buchs et al. teaches a product that is identical to what is instantly claimed, then the process limitations, while considered, are not patentably *limiting* to the claims because the prior art teaches an identical product and, therefore, the manner in which it was made fails to apparently result in a product different from that which is already known in the prior art.

Buchs et al. teaches a concentrated stable solution, especially an injection solution characterized in that it contains besides water either sodium-leucovorin or potassium-leucovorin or sodium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid or potassium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid (col.2, lines 15-19). Buchs et al. teaches that N(5)-Formyl-5,6,7,8-tetrahydrofolic acid, also named folinic acid, is used in the form of its calcium salt (calcium-leucovorin USP) as an agent in the cancer chemotherapy (col.1, lines 9-11). Buchs et al. teaches the method of preparation of the concentrated stable solution especially an injection solution where in Folinic acid or N (5)-methyl-5, 6, 7, 8-tetrahydrofolic acid is suspended in degassed water at room temperature under an inert gas atmosphere. The water is acceptable for the preparation of injection solutions.

An aqueous solution of sodium- or potassium-hydroxide, -hydrogen carbonate or -carbonate is added in portions for a sufficient time until a clear solution is formed, which has the desired pH-value. The obtained solution is subjected to sterile filtration, and vials are filled with the resulting sterile solution under an inert gas atmosphere (col. 2, lines 20-32, patented claim 11).

Buchs et al. teaches that the preferred embodiments of his invention comprised more preferably from 2-6% weight of sodium-leucovorin or potassium-leucovorin or sodium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid or potassium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid (col.2, lines 33-39, patented claims 4- 5 and 13-15). Buchs et al. also teaches that the pH-value of the solution is more preferably 8.0 (col.2, line 40-41, patented claims 6-8 and 16) Buchs et al. additionally teaches that his invention also provides a concentrated, stable solution of the bases of folates, which contains neither a stabilizer nor complexing agents (col.2, lines 9-11). Note: It is a position of the examiner that the use of term “completing” in col.2, line 11 is a typo and is actually referring to the “complexing” agent, since the reference discloses that EDTA and similar complexing agents are not acceptable in an injection solution and it is the object of the invention to overcome that drawback in the prior art. Additionally the example of the preparation of the inventive solution does not include any stabilizing and complexing agent (page 2, line 65 to page 3, line 17). Buchs et al. additionally teaches in example the preparation of inventive solution which comprises the following steps, 200.7 g of folinic acid with a water content of 10.2% by weight were suspended under stirring at room temperature in 2.5 liters of degassed, sterile water under a nitrogen atmosphere. Then was added

drop by drop under stirring a 10% aqueous sodium hydroxide solution until a clear solution has been formed, which had a pH-value of 8.0. The obtained clear solution was diluted to a volume of 3.6 liters by the addition of degassed, sterile water. This diluted solution was subjected to a sterile filtration (pore size: 0.2 micrometer). The obtained sterile filtrate was filled under a nitrogen atmosphere in vials. The vials were stored in a refrigerator at a temperature of 4.degree. C (page 2, line 65 to page 3, line 17). Buchs et al. also teaches that the solution of his invention can be used in the preparation of a medicament for rescues/rescue agents after treatments with high doses of methotrexate or combined with 5-fluorouracil or used in the preparation of a medicament for the treatment of megaloblastic anemia and dihydropteridin reductase deficiency (col. 2, lines 56-62 and patented claims 17-20).

Buchs et al. does not teach their inventive concentrated folinate solution to comprise a diastereoisomeric excess of the (6S) sodium-folinate or potassium folinate.

However, Mueller et al. teaches the preparation methods to synthesize sodium (6S) folinate and potassium (6S) folinate (abstract). Mueller et al. teaches that synthetic folinic acid consists of a 1:1 mixture of the two diastereomers R and S (col. 1, lines 29-31) where as in the natural state, for example in the liver folinic acid is found only in the S form and further teaches that the inverse (R) form is barely metabolized and is slowly eliminated through the urine and is biologically inactive (col.1, lines 35-49). Mueller et al. teaches the preparation of sodium (6S) folinate by a method using calcium (6S) folinate using a cation exchanger resin (example 4, col.5) and potassium folinate by dissolving (6S) folinic acid in aqueous potassium hydroxide (example 5, col.6), Mueller et al.

teaches that the (6S) sodium and potassium folinate has comparatively good water solubility and high tolerance and is therefore appropriate starting material for preparation of injectable solutions (col.3, lines 34-42).

Accordingly, the injection solution of sodium and potassium folinate as taught by Buchs et al. in view of the teachings of Mueller et al. renders the instantly claimed invention prima facia obvious. Buchs et al. expressly teaches concentrated injectable solution comprising sodium or potassium folinate. Mueller teaches that the R form of folinate is not active and provides a method of preparing pure sodium (6S) folinate. It would have been obvious to a person of ordinarily skill in the art to utilize the purified (6S) sodium folinate taught by Mueller et al. in the concentrated solution of Buchs et al. A person of ordinary skill would have been motivated to do such a substitution from the prior art knowledge that the S version of folinate is the active form and the R version is inactive and the substitution will yield solution which therefore would have better activity and bioavailability. As such a person of ordinary skill in art would be imbued with a reasonable expectation of success in developing a concentrated injectable solution with just the 6(S) form of sodium folinate instead of the racemic form as the concentrated injectable solution with the racemic form is taught in the prior art and the procedure for the preparation of the 6(S) form of sodium folinate is known in the prior art and all that is required is the simple substitution of the racemic form with the active 6(S) form of sodium or potassium folinate.

In addition, It has been determined that pure optical isomer is unpatentable over racemic mixture unless it possess unexpected properties not possessed by racemic

mixture. *In re Anthony,* 414, F.2nd 1383, 162 USPQ 594 and that in absence of unobviousness, one cannot patent optical isomer over racemate, *Brever v. Ladd,* 147 USPQ 87. In addition it has been determined that in order to patent an optical isomer, it is necessary to show that they posses "qualities [which] are utterly unobtainable" in the racemic mixture. *Sterling Drug v. Watson*, 108 USPQ 37. Note *also Pfizer v. Int. Rectifier Corp*., 190 USPQ 273, 280; *Lilly v. Generex*, 174 USPQ 65. Accordingly, absence evidence to the contrary, the instantly claimed concentrated injection solution of sodium and potassium folinate would posses properties similar to the concentrated solution of sodium and potassium folinate for injection taught by Buchs et al. would possess similar properties and elicit actions identical to the instant It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph

It is also noted that the expectation with regard to enantiomers is that activities as they pertain to living systems are expected to be different, *In re Adamson,* 275 F.2nd 952, 125 U.S.P.Q. 233 (C.C.P.A 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving

enantiomers having substantially different pharmacological activity. It appears as though applicant has determined experimentally what a person of ordinary skill in the art would have expected, namely, that the racemic mixture of the prior art may be different () and (-) enantiomers possessing substantially different pharmacological activity. This is an expected result. It is well established that expected beneficial results are evidence of obviousness of the claimed invention just as unexpected beneficial results are evidence of unobviousness, *In re Skoll,* 523, F.2nd 1392, 186 U.S.P.Q. 481 (C.C.P.A. 1975).

Response to applicant's arguments filed on 08/27/2010:

Applicant traverses the above rejection with the following arguments:

a. Applicants recite on page 9 of their arguments that their solution of (6S)-sodium-folinate is prepared from amorphous (6S)-folinic acid which in turn is prepared form (6S)-calcium folinate. Applicants submit a declaration of Dr..Fabrizia Marazza stating that (6S) folinic acid could not be obtained following the teachings of the applied prior art in particular example 6 of EP 0,293,029 (the European counter part of Mueller et al.) and in fact following these directions were able to obtain an untreatable, rubber like products despite the fact that various parameters such as temp., conc., and reaction time was varied.

Applicant's traversal arguments for this rejection and the declaration submitted by Dr. Fabrizia Marazza have been fully considered, but are not found to be persuasive.

First, the data provided in the declaration (see translation of the lab Journal page 2248) teaches the synthesis with just a single set of parameters such as one single temperature, one single pH. No data is provided with the varying parameters of the temperature, concentration and reaction time.

Second, it is not clear from the data provided, if the (6S)-calcium folinate used by the applicants in their experiment was prepared using the same method disclosed by Mueller et al. (see Example 1 of Mueller et al., in col.3 and 4). It is well known that the quality of the starting material is critical in determining the quality of the final products. As such not knowing if the (6S)-calcium folinate used in the experiment was prepared in the same manner taught by Mueller et al. the resulting product obtained by the applicants which is the rubber like material cannot be conclusively stated as being prepared using the procedure of Mueller et al.

Finally, Mueller et al. explicitly teaches obtaining sodium (6S)-folinate having a purity of at least 95%. In addition Mueller et al. teaches that the (6S) folinates which are commercially available are prepared by the process in accordance with their invention (col.3, lines 26-31).

As such the data submitted by the applicants are not convincing and therefore arguments and the declaration submitted by the applicants is not persuasive and the rejection is maintained.

Conclusion

Claims 28-43 and 47-57 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614